
LETTERS TO THE EDITOR

Molybdenum in Human Nutrition

To the Editor:

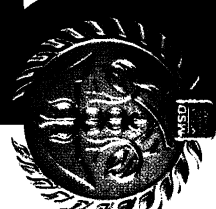
Molybdenum is classified as a trace metal among human nutrients. It is essential for good health, but there is no evidence that molybdenum deficiency is responsible for any human disease.¹ An unequivocal need for growth and maintenance in humans has not been determined.

Molybdenum is a chief constituent of the iron-containing enzyme xanthine oxidase, which breaks down purines to uric acid and is also involved in the mobilization of ferritin, storage iron, from reserves in the liver. Molybdenum is essential for xanthine oxidase activity and also for the actions of the enzymes sulfite oxidase and aldehyde oxidase. Xanthine oxidase catalyzes the transfer of hypoxanthine and xanthine to uric acid. Sulfite oxidase speeds the oxidation of sulfite to sulfate on proteins. And aldehyde oxidase oxidizes and detoxifies certain aldehydes, purine, pyrimidine, and pteridine. Both xanthine oxidase and aldehyde oxidase function in the terminal respiratory chain of oxidative metabolism in conjunction with another of their components, flavin adenine dinucleotide (FAD). Some dehydrogenases and other flavoenzymes containing molybdenum are known in microbes but have not yet been demonstrated in humans. In animals and some plants, molybdenum seems to link flavin nucleotide to protein.

Molybdenum is easily absorbed in the upper small intestine, and is

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VASERETIC[®]



(Enalapril Maleate-Hydrochlorothiazide|MSD)

Micronase®

Tablets (glyburide) Usual starting dosage
2.5 mg-5 mg once a day

CONTRAINDICATIONS: MICRONASE Tablets are contraindicated in patients with: 1. Known hypersensitivity or allergy to the drug. 2. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin. 3. Type I diabetes mellitus, as sole therapy.

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY: The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with noninsulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (Diabetes, 19 [Suppl 2]: 747-830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of MICRONASE and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

PRECAUTIONS: General—Hypoglycemia: All sulfonylureas are capable of producing severe hypoglycemia. Proper patient selection and dosage and instructions are important to avoid hypoglycemic episodes. Renal or hepatic insufficiency may increase the risk of serious hypoglycemic reactions. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency, are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Loss of Control of Blood Glucose: In diabetic patients exposed to stress such as fever, trauma, infection or surgery, a loss of control may occur. It may then be necessary to discontinue MICRONASE and administer insulin. Adequate adjustment of dose and adherence to diet should be assessed before classifying a patient as a secondary failure. **Information for Patients:** Patients should be informed of the potential risks and advantages of MICRONASE and of alternative modes of therapy. They also should be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of urine and/or blood glucose. The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure should also be explained.

Laboratory Tests: Response to MICRONASE Tablets should be monitored by frequent urine glucose tests and periodic blood glucose tests. Measurement of glycosylated hemoglobin levels may be helpful in some patients.

Drug Interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta adrenergic blocking agents.

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Studies in rats at doses up to 300 mg/kg/day for 18 months showed no carcinogenic effects. Glyburide is nonmutagenic when studied in the Salmonella microsome test (Ames test) and in the DNA damage/alkaline elution assay.

Pregnancy, Teratogenic effects: Pregnancy Category B. Reproduction studies in rats and rabbits have revealed no evidence of impaired fertility or harm to the fetus due to glyburide. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed. Insulin should be used during pregnancy to maintain blood glucose as close to normal as possible. **Nonteratogenic Effects:** Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. MICRONASE should be discontinued at least two weeks before the expected delivery date.

Nursing Mothers: Some sulfonylurea drugs are known to be excreted in human milk. Insulin therapy should be considered.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Hypoglycemia: See Precautions and Overdosage sections. **Gastrointestinal Reactions:** Cholestatic jaundice and hepatitis may occur rarely. MICRONASE Tablets should be discontinued if this occurs. Gastrointestinal disturbances (nausea, epigastric fullness, and heartburn) occurred in 1.8% of patients during clinical trials. They were the most commonly reported adverse reactions. They tend to be dose related and may disappear when dosage is reduced. Liver function abnormalities have been reported.

Dermatologic Reactions: Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions occurred in 1.5% of patients during trials. These may be transient and may disappear despite continued use of MICRONASE; if skin reactions persist, the drug should be discontinued. **Porphyrria cutanea tarda** and photosensitivity reactions have been reported with sulfonylureas. **Hematologic Reactions:** Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas. **Metabolic Reactions:** Hepatic porphyria and disulfiram-like reactions have been reported with sulfonylureas; however, hepatic porphyria has not been reported with MICRONASE and disulfiram-like reactions have been reported very rarely. Cases of hyponatremia have been reported with glyburide and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. (SIADH) secretion has been reported with certain other sulfonylureas, and it has been suggested that these sulfonylureas may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.

OVERDOSAGE: Overdosage of sulfonylureas, including MICRONASE Tablets, can produce hypoglycemia. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate which will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, since hypoglycemia may recur after apparent clinical recovery.

Maximum Dose: Daily doses of more than 20 mg are not recommended.

Dosage Interval: Once-a-day therapy is usually satisfactory. Some patients, particularly those receiving more than 10 mg daily, may have a more satisfactory response with twice-a-day dosage.

Specific Patient Populations: MICRONASE is not recommended for use in pregnancy or for use in children. In elderly patients, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycemic reactions. (See Precautions Section).

For additional product information see your Upjohn representative.

Upjohn

THE UPJOHN COMPANY, Kalamazoo, MI 49001

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transported attached to proteins in blood for tissue storage and use as an enzyme cofactor. The metal is transported to the liver by red blood cells.² Concentrations in human whole blood range from 30 to 700 nmol/L and vary with the soil contents of the metal in different geographic areas. Normal values for serum molybdenum levels have not yet been established. Excretion takes place in the bile and urine. Molybdenum is secreted in the bile and then recirculated into the liver by an enterohepatic circulation with the excess appearing in the feces. About half of the total intake may be excreted in the urine. Urinary levels vary with environmental exposure to the metal and do not regulate tissue levels.

There is no storage site for molybdenum in humans, but the highest concentrations are found in the liver, bones, adrenals, kidneys, small intestine, and skin.³ The molybdenum content of animal organs is extremely low. In humans, the kidney contains about 1.6 parts per million, the liver about 3.29, and spleen, lung, and brain from 0.14 to 0.20.

Molybdenum Requirements. The amount of molybdenum required by humans is not established; there is recommended dietary allowance. The Food and Nutrition Board of the National Academy of Sciences advises that deficiency, although well documented in animals, has never been observed in humans. The Board's estimated safe and adequate dietary intake is 0.15 to 0.50 mg for adults, 0.05 to 0.15 mg for adolescents, and 0.03 to 0.08 mg for infants.⁴ The parenteral needs for ammonium molybdenate are from 20 to 30 µg per day. Most physicians will not add molybdenum to the feeding solution for patients on total parenteral nutrition until a definite need is demonstrated.

Dietary Molybdenum. The amount

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ZANTAC® 150 Tablets
(ranitidine hydrochloride)**ZANTAC® 300 Tablets**
(ranitidine hydrochloride)

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

INDICATIONS AND USAGE: ZANTAC® is indicated in:

1. Short-term treatment of **active duodenal ulcer**. Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer**. Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD)**. Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.

2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella*, *Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocellular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 tablets (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

Glaxo

Glaxo Inc.
Research Triangle Park, NC 27709

BRIEF SUMMARY

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of molybdenum in plants depends greatly on the content in the soil, which varies geographically and with soil type. The molybdenum content is low in plants grown in acid, sandy soils and higher in those grown in alkaline or neutral soils with a high proportion of organic matter. Therefore, dietary molybdenum also varies considerably. Average daily intake ranges from 0.1 to 0.46 mg,⁵ although extremes range from 0.05 to 0.53 mg daily.⁶ The best food sources of molybdenum, with approximately 0.6 parts per million include legumes, whole grains, animal organ meat, dark green leafy vegetables, and milk.

Molybdenum Deficiency.

Molybdenum is a copper antagonist.^{7,8} Like zinc, excess molybdenum interferes with copper absorption. In livestock, copper and molybdenum prevent the uptake of excessive amounts of each other, but only in the presence of inorganic sulfate. Molybdate absorption is inhibited by sulfate. It is suspected that in the United States, the relatively high copper intake in humans also inhibits both molybdenum and iron absorption. Some members of animal species with a molybdenum-deficient diet do not grow normally. In rats and chickens fed molybdenum-deficient diets, xanthine oxidase activity in the intestine, but not liver, is decreased.⁹ Hepatic xanthine oxidase activity may be reduced, however, upon addition of tungsten, a competitive inhibitor of molybdenum, to the animals diets. In goats and minipigs, molybdenum deficiency without tungsten in the diets, produces anorexia, depressed growth and reproduction, elevated copper levels in the liver and brain, and increased mortality. Molybdenum-responsive growth depression in lambs and poultry proves that a reversible, spontaneously developing deficiency syndrome in

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May 1988

CALENDAR

February 1990

Activities in Honor of Black History Month.

February 16-20, 1990

Region I-NMA Annual Scientific and Business Meeting. Medicine in the Nineties and Beyond. Barbados. Travel plus lodging \$799. Call Astral Travel 718-629-2222. For information, call 201-672-7972.

March 2-4, 1990

NMA Board of Trustees. Las Vegas Bally's Casino Resort, Las Vegas, Nevada.

April 27-29, 1990

NMA Board of Trustees. Washington, DC.

May 3-7, 1990

Fifth International Interdisciplinary Conference on Hypertension in Blacks. Longbeach, California. Call 404-589-3810.

May 25-27, 1990

Tentative Date for Annual Meeting of Region II-NMA, Atlantic City, New Jersey.

June 1990

The Volunteer State Medical Association 86th Annual Scientific Session. Memphis, Tennessee. Call 901-527-1153.

July 9-12, 1990

National Assembly on Addictive Disorders: Enlisting Scientific Knowledge in the War on Drugs. Sponsored by the Vesper Society Group, AMA, APHA, and others. Washington, DC area. (Tentative) Call 415-633-0666.

July 28-August 2, 1990

The 95th Annual Convention and Scientific Assembly of the National Medical Association. Bally Grand Hotel, Las Vegas, Nevada.

November 1990

85th Anniversary Banquet of the Provident Clinical Society of Brooklyn. Brooklyn, New York.

FUTURE

July 1991

The 96th Annual Convention of NMA. Indianapolis, Indiana.

July or August 1991

The 6th International Interdisciplinary Conference on Hypertension in Blacks. Brazil.

July 1992

The 97th Annual Convention of NMA. Hawaii.

Send information about coming events for the Calendar to Theresa Greene Reed, MD, MPH, 11516 Patapapsco Dr., Rockville, Maryland 20852 or call 301-468-6830.

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animals exists.¹⁰ Nonetheless, it is neither necessary nor advisable to supplement diets of animals with the metal.

As mentioned, there is no spontaneous molybdenum deficiency syndrome in humans.¹¹ In various experimental situations, the following signs and symptoms have been reported: tachycardia, night blindness, irritability, headaches, nausea, lassitude and lethargy, coma, decreased xanthine oxidase activity in the intestine and liver, impaired purine metabolism (hypoxanthine and xanthine cannot be converted to uric acid), and abnormal biochemistry of

sulfur-containing proteins.

A molybdenum deficiency syndrome in a young man on total parenteral nutrition for 18 months was described.¹² He experienced severe headache, nyctalopia, tachycardia, tachypnea, nausea, vomiting, central scotoma, lethargy, disorientation, and coma. Hypouricemia was marked and accompanied by raised plasma methionine levels. Conversion of sulfite to sulfate was impaired, with accumulation of sulfite, which is toxic to the central nervous system. Urinary excretion as the oxypurines xanthine, and hypoxanthine, was impaired. These metabolic abnormalities were probably secondary to decreased activities of the molybdenum-

dependent enzymes, xanthine oxidase and sulfite oxidase. Addition of 300 µg of ammonium molybdenum to the nutritional solution daily corrected the biochemical and clinical finding.

Molybdenum Excess. Dental caries rates are lower in areas where children consume higher amounts of molybdenum.¹³ This finding is consistent with a well-established cariostatic effect of the metal in animals. Whether dental caries in children is increased in subclinical molybdenum deficiency is unknown.

Molybdenum toxicity has been reported in one Russian province where an intake of 10 to 15 mg of the

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Catapres-TTS[®]

(clonidine)/TRANSDERMAL
THERAPEUTIC SYSTEM

Programmed delivery *in vivo* of 0.1, 0.2 or 0.3 mg clonidine per day, for one week.

Brief Summary of Prescribing Information

CONTRAINDICATIONS Catapres-TTS[®] (clonidine) should not be used in patients with known hypersensitivity to clonidine or to any other component of the adhesive layer of the therapeutic system.

PRECAUTIONS *General:* In patients who have developed localized contact sensitization to Catapres-TTS[®] (clonidine), substitution of oral clonidine hydrochloride therapy may be associated with development of a generalized skin rash.

In patients who develop an allergic reaction to Catapres-TTS[®] that extends beyond the local patch site (such as generalized skin rash, urticaria, or angioedema) oral clonidine hydrochloride substitution may elicit a similar reaction.

As with all antihypertensive therapy, Catapres-TTS[®] should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, or chronic renal failure.

Transdermal clonidine systems should be removed before attempting defibrillation or cardioversion because of the potential for altered electrical conductivity that may enhance the possibility of arcing, a phenomenon associated with the use of defibrillators.

Withdrawal: Patients should be instructed not to discontinue therapy without consulting their physician. Sudden cessation of clonidine treatment has resulted in subjective symptoms such as nervousness, agitation and headache, accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma, but such occurrences have usually been associated with previous administration of high oral doses (exceeding 1.2 mg/day) and/or with continuation of concomitant beta-blocker therapy. Rare instances of hypertensive encephalopathy and death have been reported.

An excessive rise in blood pressure following Catapres-TTS[®] discontinuance can be reversed by administration of oral clonidine or by intravenous phentolamine. If therapy is to be discontinued in patients receiving beta-blockers and clonidine concurrently, beta-blockers should be discontinued several days before cessation of Catapres-TTS[®] administration.

Perioperative Use: As with oral clonidine therapy, Catapres-TTS[®] therapy should not be interrupted during the surgical period. Blood pressure should be carefully monitored during surgery and additional measures to control blood pressure should be available if required. Physicians considering starting Catapres-TTS[®] therapy during the perioperative period must be aware that therapeutic plasma clonidine levels are not achieved until 2 to 3 days after initial application of Catapres-TTS[®].

Information for Patients: Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of a potential sedative effect of clonidine. Patients should be cautioned against interruption of Catapres-TTS[®] therapy without a physician's advice. Patients should be advised that if the system begins to loosen from the skin after application, the adhesive overlay should be applied directly over the system to ensure good adhesion over its 7-day lifetime. Instructions for using the system are provided. Patients who develop moderate or severe erythema and/or localized vesicle formation at the site of application, or a generalized skin rash, should consult their physician promptly about the possible need to remove the patch.

Drug Interactions: If a patient receiving clonidine is also taking tricyclic antidepressants, the effect of clonidine may be reduced, thus necessitating an increase in dosage. Clonidine may enhance the CNS-depressive effects of alcohol, barbiturates or other sedatives. Amitriptyline in combination with clonidine enhances the manifestation of corneal lesions in rats.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 132-week (fixed concentration) dietary administration study in rats, Catapres[®] (clonidine HCl) administered at 32 to 46 times the oral maximum recommended daily human dose (MRDHD) was unassociated with evidence of carcinogenic potential. Results from the Ames test with clonidine hydrochloride revealed no evidence of mutagenesis. Fertility of male or female rats was unaffected by clonidine doses as high as 150 mcg/kg or about 3 times the oral MRDHD. Fertility of female rats did, however, appear to be affected (in another experiment) at the dose levels of 500 to 2000 mcg/kg or 10 to 40 times the oral MRDHD.

Pregnancy/Teratogenic Effects **PREGNANCY CATEGORY C:** Reproduction studies performed in rabbits at doses up to approximately 3 times the oral maximum recommended daily human dose (MRDHD) of Catapres[®] (clonidine HCl) have revealed no evidence of teratogenic or embryotoxic potential in rabbits. In rats, however, doses as low as 1/3 the oral MRDHD of clonidine were associated with increased resorptions in a study in which dams were treated continuously from 2 months prior to mating. Increased resorptions were not associated with treatment at the same or at higher dose levels (up to 3 times the oral MRDHD) when dams were treated days 6-15 of gestation. Increased resorptions were observed at much higher levels (40 times the oral MRDHD) in rats and mice treated days 1-14 of gestation (lowest dose employed in the study was 500 mcg/kg). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: As clonidine is excreted in human milk, caution should be exercised when Catapres-TTS[®] (clonidine) is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of twelve have not been established.

ADVERSE REACTIONS Most systemic adverse effects during therapy with Catapres-TTS[®] (clonidine) have been mild and have tended to diminish with continued therapy. In a 3-month, multicenter trial of Catapres-TTS[®] in 101 hypertensive patients, the most frequent systemic reactions were dry mouth (25 patients) and drowsiness (12 patients).

Transient localized skin reactions, primarily localized pruritus, occurred in 51 patients. Twenty-six patients experienced localized erythema. This erythema and pruritus were more common in patients utilizing an adhesive overlay for the entire 7-day treatment period. Allergic contact sensitization to Catapres-TTS[®] was observed in 5 patients.

In additional clinical experience, contact dermatitis resulting in treatment discontinuation was observed in 128 of 673 patients (about 19 in 100) after a mean duration of treatment of 37 weeks. The incidence in white females was about 34 in 100; in white males about 18 in 100; in black females about 14 in 100; and in black males about 8 in 100.

The following less frequent adverse experiences were also reported in patients involved in this multicenter trial with Catapres-TTS[®]:

Gastrointestinal: Constipation (1 patient); nausea (1); and change in taste (1).

Central Nervous System: Fatigue (6 patients); headache (5); lethargy (3); sedation (3); insomnia (2); dizziness (2); and nervousness (1).

Genitourinary: Impotence/sexual dysfunction (2 patients).

Dermatological: Localized vesiculation (7 patients); hyperpigmentation (5); edema (3); excoriation (3); burning (3); papules (1); throbbing (1); blanching (1); and generalized macular rash (1).

In additional clinical experience involving 3539 patients, less common dermatologic reactions have occurred, where a causal relationship to Catapres-TTS[®] was not established: maculopapular skin rash (10 cases); urticaria (2 cases); angioedema involving the face (2 cases), one of which also involved the tongue.

Oro-tolaryngeal: Dry throat (2 patients).

In long experience with oral Catapres[®], the most common adverse reactions have been dry mouth (about 40%), drowsiness (about 35%) and sedation (about 8%). In addition, the following adverse reactions have been reported less frequently:

Gastrointestinal: Nausea and vomiting, about 5 in 100 patients; anorexia and malaise, each about 1 in 100; mild transient abnormalities in liver function tests, about 1 in 100; rare reports of hepatitis; parotitis, rarely.

Metabolic: Weight gain, about 1 in 100 patients; gynecocystic mastitis, about 1 in 1000; transient elevation of blood glucose or serum creatine phosphokinase, rarely.

Central Nervous System: Nervousness and agitation, about 3 in 100 patients; mental depression, about 1 in 100 and insomnia, about 5 in 1000. Vivid dreams or nightmares, other behavioral changes, restlessness, anxiety, visual and auditory hallucinations and delirium have been reported.

Cardiovascular: Orthostatic symptoms, about 3 in 100 patients; palpitations and tachycardia, and bradycardia, each about 5 in 1000. Raynaud's phenomenon, congestive heart failure, and electrocardiographic abnormalities (i.e. conduction disturbances and arrhythmias) have been reported rarely. Rare cases of sinus bradycardia and atrioventricular block have been reported, both with and without the use of concomitant digitalis.

Dermatological: Rash, about 1 in 100 patients; pruritus, about 7 in 1000; hives, angioneurotic edema and urticaria, about 5 in 1000; alopecia, about 2 in 1000.

Genitourinary: Decreased sexual activity, impotence and loss of libido, about 3 in 100 patients; nocturia, about 1 in 100; difficulty in micturition, about 2 in 1000; urinary retention, about 1 in 1000.

Other: Weakness, about 10 in 100 patients; fatigue, about 4 in 100; headache, and discontinuation syndrome, each about 1 in 100; muscle or joint pain, about 6 in 1000 and cramps of the lower limbs, about 3 in 1000. Dryness, burning of the eyes, blurred vision, dryness of the nasal mucosa, pallor, weakly positive Coombs' test, increased sensitivity to alcohol and fever have been reported.

HOW SUPPLIED Catapres-TTS[®]-1 (clonidine) and Catapres-TTS[®]-2 are supplied as 4 pouched systems and 4 adhesive overlays per carton, 3 cartons per shipper (NDC 0597-0031-12 and 0597-0032-12, respectively). Catapres-TTS[®]-3 is supplied as 4 pouched systems and 4 adhesive overlays per carton (NDC 0597-0033-34).

| | Programmed Delivery Clonidine <i>in vivo</i> per Day Over 1 Week | Clonidine Content | Size | Code |
|------------------------------|--|----------------------|----------------------|-------|
| Catapres-TTS [®] -1 | 0.1 mg | 2.5 mg | 3.5 cm ² | BI-31 |
| Catapres-TTS [®] -2 | 0.2 mg | 5.0 mg | 7.0 cm ² | BI-32 |
| Catapres-TTS [®] -3 | 0.3 mg | 7.5 mg | 10.5 cm ² | BI-33 |

Consult package insert before prescribing. CT-BPI-7/88

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metal is ingested daily by some of the inhabitants. A syndrome resembling gout develops, along with high uric acid levels in the serum arthropathy, and renal involvement. Serum xanthine oxidase activities, molybdenum levels, and urinary copper excretion are all high.¹⁴ The syndrome only develops when high amounts of molybdenum are consumed with a normal copper intake. When dietary copper is increased, the gout syndrome does not materialize. This is another example of the reciprocal inhibition between the two metals.¹⁴ The relatively higher exposures of molybdenum in the American diet are not believed to increase the incidence of gout, in part because of higher simultaneous copper intake in the United States.

High molybdenum and low copper intake is suspected in some cases of genu valgum, usually caused by fluorosis in central and southern India.¹⁵ Molybdenum increases fluoride absorption and retention in muscle and brain.¹⁶

Conclusion. Molybdenum is an essential trace element plentiful in food, and a balanced diet will provide all the molybdenum needed for normal function at all levels of activity. Multivitamin supplements commonly contain the metal, typically 15 µg, in the form of yeast, per tablet or capsule. This practice is unnecessary. A high normal daily intake of molybdenum (0.54 mg), compromises copper balance and, therefore, molybdenum supplementation may be harmful.

Calorie-restricted diets are now common in the United States, especially among women. Depending on the severity of restriction, molybdenum deficiency could theoretically develop, although this result is unlikely.

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